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Factor XI Deficiency in Women

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Factor XI (FXI) deficiency is an uncommon autosomally transmitted coagulopathy found predominantly in Jewish kindreds. It is associated with variable bleeding tendency that usually manifests after trauma, surgery, or other challenges to hemostasis. Therefore, women with FXI deficiency are at risk of excessive bleeding during their menstrual periods, childbirth, and after surgery. Increased awareness and close collaboration among hematologists, obstetricians, and gynecologists and availability of management guidelines is essential to minimize these risks. This review provides data from current research in FXI deficiency and pregnancy care, menstrual problems, and the role of screening for this disorder in women referred with menorrhagia. Am. J. Hematol. 60:48–54, 1999.

Key words: factor XI; pregnancy; menstruation

INTRODUCTION

Factor XI (FXI) deficiency was originally described in a Jewish family in the USA and was called ''hemophilia C'' and distinguished from hemophilia A or B by its occurrence in either sex and the absence of spontaneous bleeding [1]. FXI deficiency is particularly common in Ashkenazi Jews. It is one of the most common genetic disorders in this population with a heterozygous frequency of 8% [2]. In the United Kingdom (UK), FXI deficiency is responsible for 3% of all patients with a bleeding disorder on the Hemophilia Centre Directors' national register and a significant number of them have no known Jewish roots [3] but its frequency in non-Jews is unknown. Because patients with severe or partial FXI deficiency do not suffer from spontaneous bleeding but may do so only after hemostatic challenge, this bleeding disorder is probably underdiagnosed. Women are exposed to a hemostatic challenge every month during their menstrual period. The other common challenge for women is childbirth. However, the bleeding problems associated with these common events have not been well addressed because women are expected to lose blood during menstruation and after childbirth. There is also difficulty in the objective assessment of blood loss in these situations, especially menstrual blood loss [4–6]. Herein, we review FXI deficiency in women, with particular emphasis on menstruation, pregnancy, and childbirth.

INHERITANCE OF FXI DEFICIENCY AND PRECONCEPTIONAL COUNSELING

FXI deficiency was initially considered to be an autosomal dominant disorder with variable expression [1,7,8]. However, the availability of the one-stage FXI assay [9] made distinction between severe (homozygous or compound heterozygous) and partial (heterozygous) FXI deficiency possible [9,10]. At that time, it was thought that heterozygotes have no bleeding tendency [11] and therefore, autosomal recessive mode of inheritance was widely reported. However, doubt was also cast on this mode of inheritance by description of families who did not fit this pattern [7,8]. The lack of absolute relationship between FXI levels, bleeding tendency, and presence of bleeding symptoms was noticed by Leiba et al., 1965 [10]. This was later confirmed by others, and between one third to one half of heterozygous individuals were shown to bleed excessively [12–15]. In a study of 164 individuals from 20 Jewish and four non-Jewish families by Bolton-Maggs et al., 1988 [13], the inheri-

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tance was confirmed to be autosomal with severe deficiency in homozygotes and partial deficiency in heterozygotes. FXI level is <15 iu/dl in homozygous or compound heterozygotes for FXI gene mutation [13,16] and between 15–20 iu/dl and the lower limit of normal range in heterozygotes [13,17]. There is a clear demarcation in FXI levels between homozygotes and heterozygotes and a small overlap between the heterozygotes and normal [13]. Probability of heterozygosity at different FXI levels has been constructed on a chart, from which the chance of an individual being a heterozygote can be calculated if the prior probability is assessed from pedigree analysis [13]. The risk of vertical transmission of severe FXI deficiency can thus be calculated for parents in FXI-deficient families during their preconceptional counseling.

Several genetic mutations causing FXI deficiency have been described [18–21]. In the Ashkenazi Jews, FXI deficiency is caused by type II (a stop condon in exon 5) or type III (a single base change in exon 9) mutations in most kindreds [2,16,22]. These mutations are detected by polymerase chain reaction and restriction enzymes [16,22] which make carrier detection and prenatal diagnosis possible in this population. However, the situation is different in non-Jews because of the larger number of mutations causing FXI deficiency in this group.

BLEEDING TENDENCY AND FXI LEVEL

It is well recognized that there is a poor correlation between FXI level and bleeding tendency in patients with FXI deficiency [10,12–15]. Some patients with severe deficiency may not bleed at all following trauma, whereas some heterozygotes have excessive bleeding after challenge. The bleeding tendency may also vary in the same individual following hemostatic challenge [2]. The patient's genotype, site of the surgery, and the presence of additional coagulation factor defects, most commonly von Willebrand disease (vWD), can all influence the patient's bleeding tendency. Patients with genotype III/III have a less severe bleeding tendency than genotypes II/II or II/III [2]. Bleeding is much more common after intervention in tissues with high fibrinolytic activity e.g., oral and nasal cavity and genitourinary system [2,22]. In a study from Israel, most of the bleeding in partial FXI deficiency could be explained by the presence of associated vWD [23]. In UK, there is a significantly lower vWF level in partially deficient patients with a bleeding history compared with nonbleeders; however, there is no increased incidence in vWD over that expected in the general population [13].

Recent in vitro studies have thrown light on the puzzling lack of correlation between bleeding observed in these patients and the level of clotting factor [24]. The revised model of the hemostatic process suggests that although the factor VIIa/tissue factor complex initiates fibrin clot formation through the activation of factor IX and its cofactor factor VIII, factor XI has a role in sustaining hemostasis. This is enabled by the activation of factor XI by both the thrombin already generated and also through autoactivation with factor XIa.

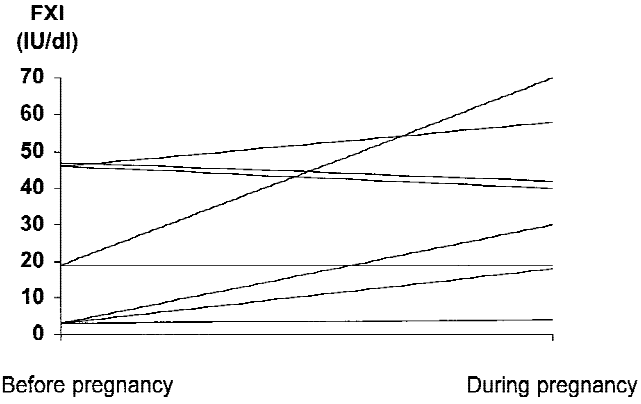

Fig. 1. Changes of FXI in FXI-deficient patients in pregnancy.

PREGNANCY, LABOR, AND FXI DEFICIENCY

The Mother

The changes in plasma level of FXI during pregnancy in FXI-deficient patients have not been studied extensively, and controversial results have been published in normal pregnant women, some studies showing an increase [25] and others a fall in levels with advancing gestation [26,27]. In our center, FXI level was assessed during second/third trimester of pregnancy in eight patients with FXI deficiency. The changes were inconsistent, as there was some increase in four patients and a slight decrease in the remaining four, but overall the changes were statistically insignificant [28] (Fig. 1). Women may be exposed to various hemostatic challenges in pregnancy e.g., invasive prenatal diagnostic techniques, termination of pregnancy, or spontaneous abortion. These procedures can be complicated by excessive and prolonged hemorrhage [3,28]. It is important therefore that factor levels are checked before these procedures and replacement therapy arranged for all homozygotes and heterozygotes with a clear history of abnormal bleeding and low levels. Because of the interindividual variability of FXI changes during pregnancy (Fig. 1) and the fact that it may not be possible to measure FXI level in emergency situations, it is recommended that this should be checked at the initial visit, and during the third trimester of pregnancy. Monitoring during the third trimester is particularly essential because it can help plan the management during labor and delivery.

The superiority of regional analgesia/anesthesia has led to its wide-spread use in labor and operative deliveries. Their use in patients with bleeding disorders has always been controversial because of the risk of spinal hematoma causing acute spinal cord compression and irreversible paraplegia. However, in patients with inherited bleeding disorders, provided that the coagulation studies are within the normal limits at the time of the procedure, there should be no contraindication to a regional block [29,30]. In FXI deficiency, this matter may be more controversial because of the rarity of the condition and poor correlation between bleeding tendency and FXI level [13]. It has been recommended that a minimum FXI plasma concentration of 20–30 iu/dl is required to maintain hemostasis during regional blocks [31]. In our center, we recommend against these procedures in homozygotes especially those with FXI level <10 iu/dl. In heterozygotes, each case should be assessed individually after careful bleeding history is taken and coagulation status is assessed. Provided the FXI level is maintained >50 iu/dl during placement and removal of the epidural catheter, these patients, especially the nonbleeders, should not be denied the benefit of these techniques. In our series, regional analgesia/anesthesia for labor or cesarean section was used in two heterozygous patients (both nonbleeders, FXI level >50 iu/dl and without prophylactic therapy) with no complications [28].

The risk of excessive bleeding after miscarriage or childbirth in FXI-deficient patients has been recognized. In severely deficient women (FXI level <11 iu/dl), a risk of 21% has been reported [13]. In heterozygotes, 17/36 pregnancies among those who were classified as ''bleeders'' were associated with excessive bleeding after a miscarriage or childbirth compared with no bleeding complications in 36 pregnancies in ''nonbleeders'' [3]. We have recently reviewed 25 births among 11 patients with FXI deficiency and reported a 16% incidence of primary postpartum hemorrhage (PPH) [28], compared with 5% in the general obstetric population [32]. The incidence of secondary PPH was even higher (24%) [28]; the incidence of secondary PPH in a general obstetric population is reported to be 0.7% [33].

Pregnancy and labor should be managed in close collaboration with the local hemophilia center and in a unit where facilities for FXI monitoring and provision of replacement treatment i.e., fresh frozen plasma or FXI concentrate, are readily available. Severely deficient individuals and heterozygotes with a clear history of abnormal bleeding and low FXI level usually require blood product support for labor, especially if delivery is operative. There is no clear consensus on the level of FXI required for hemostasis during surgical procedures [34] and it may depend on the type and the site of surgery. However, it has been suggested that a nadir of 45 and 30 iu/dl should be the aim for major and minor surgery, respectively [2]. In our center, we aim at maintaining FXI level >50 iu/dl during labor and for 3–4 days after vaginal delivery and 7 days after Caesarean section. It is very common for FXI-deficient patients to present with prolonged intermittent secondary PPH. Of six secondary incidences of PPH reported among our patients, five had intermittent moderate bleeding [28]. In these situations, we recommend administration of tranexamic acid. Tranexamic acid is a fibrinolytic inhibitor that competitively inhibits the activation of plasminogen and noncompetitively inhibits plasmin thus counteracting increased fibrinolysis in the uterus [35]. Its use in secondary PPH associated with coagulation defects has also been recommended by Bonnar et al., 1980 [35].

Traditionally, for replacement therapy and management of bleeding complications in patients with FXI deficiency fresh frozen plasma (FFP) has been used. However, since 1985, an FXI concentrate (Bio Products Laboratory, Elsatree, UK) has been available on a named patient basis. FFP is effective in raising FXI levels with a half-life of 60–80 hr but has the limitations of volume overload when large volumes need to be transfused, risk of viral transmission, and allergic reactions. FXI concentrate is virally inactivated by heating to 80°C for 72 hr and is clinically effective with a mean half-life of 52 hr [34]. However, there has recently been increasing concern regarding its thrombogenicity [15,36]. At the Royal Free Hospital, two severe cardiac complications and an episode of pulmonary embolization have been reported [15]. One of the patients with cardiac complication and the patient who suffered pulmonary embolus had other risk factors. Cramping calf pains immediately following FXI infusion was reported in another three cases. Normal pregnancy is associated with major changes in the coagulation and fibrinolytic system with an increased thrombotic potential which is marked around term and immediate postpartum period [37]. This risk is further increased with increased maternal age (a 60-fold increase in risk over age 40 compared with age less than 25 years), parity (Para 4 or more), obesity (>80 Kg), pregnancy complicated by preeclampsia, prolonged hospitalization and immobility, presence of antiphospholipid antibodies, after prolonged labor, instrumental and cesarean deliveries with greater increase after emergency cesarean sections [38]. Therefore, the potential risks and benefits of FFP or FXI concentrate should be carefully assessed individually when FXI replacement therapy is considered. In addition to the long-term complications, exposure to virally contaminated products during pregnancy also has the risk of vertical transmission and fetal infection. Therefore, in younger patients with no additional thrombotic risk factors, FXI concentrate may still be the treatment of choice for invasive procedures during pregnancy, labor, and cesarean sections. However, in patients with high risk of thrombosis, we recommend treatment

with FFP or possibly FXI concentrate products in association with low molecular weight heparin prophylaxis depending on balance of risks. The dose of FXI concentrate products should not exceed 30 iu/kg with the aim of raising FXI level to no greater than 70 iu/dl. Concurrent use of tranexamic acid and other antifibrinolytic drugs should also be avoided [39]. It is therefore recommended that treatment with these products should be in collaboration with a hemophilia treatment center [40] and monitoring of thrombotic markers [39].

The Fetus/Neonate

Affected fetuses are potentially at risk of hemorrhage during labor and delivery because of their exposure to various hemostatic challenges including invasive monitoring techniques, the birth process, and instrumental deliveries. The effect of mode of delivery on the risk of perinatal bleeding has not been studied in FXI deficiency because of the rarity of this condition. However, in affected male hemophiliac it has been shown that the risk of serious bleeding in normal vaginal delivery is small and that delivery of all fetuses known to be at risk of hemophilia by cesarean section is not expected to eliminate the risk. However, in the same study the use of vacuum extraction was shown to constitute a significant risk factor of serious subgaleal/cephalic hematoma and intracranial hemorrhage [41]. The association of intracranial hemorrhage with instrumental deliveries in male haemophiliac was also reported by Kletzel et al. (1989) [42]. Therefore, it is recommended that fetuses at risk of being affected by FXI deficiency or any other bleeding disorder should be delivered by the least traumatic method. Prolonged labor, and especially prolonged second stage of labor should be avoided and early recourse to cesarean section should be considered. Although vacuum extraction should not be used, low forceps delivery may be considered less traumatic than cesarean section when the head is deeply engaged in the pelvis and delivery can be achieved as an easy outlet procedure and performed by an experienced obstetrician. Mid-cavity forceps and forceps involving the rotation of the head should be avoided.

Although fetuses affected by any bleeding disorder are potentially at risk of scalp hemorrhage from the use of fetal scalp electrode and fetal blood sampling for intrapartum monitoring, there is lack of published data to support this. No bleeding complication in affected fetuses and neonates has been reported so far from these procedures. Perhaps they have not been used frequently in these situations. However, it is probably advisable to avoid their use in fetuses at risk.

At the time of delivery, an anticoagulated sample of cord blood should be collected and sent to the hemophilia laboratory within 2 hr of collection for investigation. When assessing the neonatal FXI level it should be appreciated that the level is low at birth and correlates with gestational age [26,43] and reaches adult levels at the age of 6 months [44]. Mean values of 38 iu/dl, 53 iu/dl, and 69 iu/dl have been reported at day 1, day 30, and day 90 of age for healthy full-term babies [44]. Vitamin K should be given to the neonate orally and immunization by intradermal route and hepatitis B immunization should be considered [29]. Intramuscular injections should be avoided and the parents should be advised to postpone circumcision until the diagnosis of bleeding disorders has been confirmed or refuted in the neonate.

GYNECOLOGICAL PROBLEMS IN WOMEN WITH FXI DEFICIENCY

Menorrhagia

The normal menstrual blood loss is between 20–60 ml with over 90% of the total menses being lost in the first three days [5]. Menorrhagia is defined objectively as menstrual blood loss $\geqslant$80 ml [4,45]. When the total menstrual loss exceeds 80 ml, the incidence of anemia significantly increases [46]. Inaccuracy of subjective diagnosis of menorrhagia and the need for an objective measure of menstrual blood loss are documented well [4–6]. A pictorial blood assessment chart (PBAC), a simple nonlaboratory method for objective assessment of menstrual loss has been described by Higham et al., 1990 [47]. Using a score of $\geqslant$100 as equivalent to a menstrual loss of >80 ml, has been compared with the alkaline hematin method [48] and was shown to have a reasonable accuracy, with a sensitivity of 86% and a specificity of 89%. Alkaline hematin and other laboratory methods are specialized, time-consuming techniques and inconvenient to the patients.

Hemostasis in the menstruating uterus is the result of a delicate balance between platelet aggregation, fibrin formation, vasoconstriction, and tissue regeneration on one hand, and prostaglandins induced platelet inhibition, vasodilatation, and fibrinolysis on the other [49]. Because hemostatic plug formation plays an important role in uterine hemostasis during menstruation [49], it is not surprising that there is an increased frequency of menorrhagia in patients with coagulation disorders. Many clinical reports in the literature link disorders of blood coagulation with subjectively reported menorrhagia [50,51]. In FXI deficiency, it has been described that affected women, including those with partial deficiency, are more likely to have menorrhagia than their unaffected relatives [3]. In our center, objective assessment of menstrual loss using PBAC, in patients with inherited bleeding disorders including 20 women with FXI deficiency, showed that they not only suffer from heavy menstruation but also prolonged menstrual periods (Kadir et al., submitted for publication). Menstrual bleeding was $\geqslant$5 days and $\geqslant$8 days in 83% and 25%, respectively. In the

general population, the duration of a menstrual period varies from 2–8 days with a mean of 5 days [52]. The prevalence of menorrhagia in patients with FXI deficiency was 59%, compared with the prevalence of 9% [45]–11% [4] in the general population, and 75%, 65%, and 75% of them experienced bleeding through protection, flooding at night, and passage of clots, respectively. There was no significant difference in the incidence of menorrhagia between heterozygous and homozygous women, which is in agreement with the lack of correlation between FXI levels and bleeding tendency in FXI deficient patients [13].

On the other hand, undiagnosed bleeding disorders especially in their mild forms can be a significant underlying factor in patients presenting with menorrhagia. In a study by Kadir et al., 1998 [53], the prevalence of FXI deficiency, including those with additional vWD, in patients with objectively confirmed menorrhagia was 4% (95% confidence interval 1.5–8.5%) compared with its estimated prevalence of 1/100,000 in the general population. Therefore, screening for FXI deficiency should also be considered in a patient with menorrhagia with no obvious organic cause, especially in an at-risk population e.g., women of Ashkenazi descent, before embarking on any invasive procedures.

Menorrhagia is a debilitating medical and social problem and can be a cause of embarrassment and inconvenience to many women. Menstruation in patients with inherited bleeding disorders, especially those with objectively confirmed menorrhagia, prolonged duration of menstruation, and those who experience flooding or passage of clots during menstruation has adverse effects on many aspects of life. In a study of quality of life in women with inherited bleeding disorders, 39% of women had to cut down on the time they spent on their work or other activities, 47% accomplished less than they would like, 38% were limited in the kind of work or other activities, and 40% experienced difficulties performing their work during the menstrual period (Kadir et al., submitted for publication). Therefore, we recommend that women with FXI deficiency or any other inherited bleeding disorder should be asked regularly about their periods and an objective assessment of menstrual loss should be performed by PBAC in those who complain of excessive blood loss. Those with normal PBAC scores can be reassured and appropriate investigations, treatment, and referrals to gynecologists should be arranged for those with heavy loss.

Tranexamic acid is the drug of choice in treatment of menorrhagia in FXI-deficient women. Tranexamic acid is known to significantly reduce excessive menstrual blood loss associated with inherited bleeding disorders [35], or when the cause is unknown [35,54], by its effect on endometrial fibrinolytic enzymes [55] and reduction in both plasminogen activator activity and plasmin activity in menstrual fluid [56]. Few isolated cases of intracranial thrombosis have been reported in women taking this medication [57]. However, large-scale studies have shown the safety of this medication and that the incidence of thrombosis is not greater than spontaneous thrombosis in women [58].

Nonsteroidal antiinflammatory drugs are ineffective and may increase the menstrual blood loss in the treatment of menorrhagia in patients with underlying bleeding disorders [59]. Oral combined contraceptives increase factor VIII and von Willebrand factor activity but do not affect FXI. However, they can reduce menstrual blood loss by inducing regular shedding of a thinner endometrium. Desmopressin (DDAVP) administered intranasally as a spray has been suggested to be effective in the management of menorrhagia in patients with inherited bleeding disorders [60].

Increased awareness among family doctors, gynecologists, hematologists, and other staff in the hemophilia center of the high prevalence of menorrhagia among these patients and of treatment options is necessary for the appropriate management of such patients and to improve their quality of life.

Hemorrhagic Complications Following Gynecological Operations

Gynecological operations like any other surgical procedures or injuries can be complicated by hemorrhage in patients with FXI deficiency. The bleeding can be brisk at the time of the operation and continues until treated or it begins several hours after injury and oozing persists for many days [2]. Although surgical bleeding may complicate any type of surgery in these patients, it is more frequently associated with procedures involving tissues with high plasminogen activators e.g., dental extraction, tonsillectomy, urologic, and nasal surgery compared with procedures like appendectomy, cholecystectomy, and hysterectomy [2,22,61]. Endometrium has high fibrinolytic activity and any surgical intervention even if minor may therefore be associated with risk of bleeding. Excessive bleeding has been reported after dilatation and curettage (Kadir et al., submitted for publication) [62]. In one of the patients reported by Purcell and Nossel, 1970 [62], the bleeding required administration of 11 units of blood and 36 units of FFP, hysterectomy, and 41 days of hospitalization. Endometrial ablative techniques are increasingly used for management of menorrhagia that does not respond to medical treatment. These procedures, in particular endometrial resection, are associated with risk of bleeding complications. It is therefore sensible to choose thermal or laser ablation in FXI-deficient patients.

When surgical intervention is required, the patient should be evaluated carefully and prepared in collaboration with the hemophilia center. Ingestion of aspirin or

other platelet antiaggregating agents should be avoided for at least a week before the surgery [2]. Prophylactic treatment with FFP or FXI concentrate should be considered depending on the patient's bleeding history, her FXI activity, and the nature and the site of the operation. The replacement therapy should be started before surgery and carefully monitored by FXI activity keeping FXI level ⩾30 iu/dl for 5 days and ⩾45 iu/dl for 10–14 days for minor and major surgery, respectively [2]. A technique with least blood loss should be chosen. Bleeding vessels should be ligated and not cauterized because oozing can occur after surgery [2]. It is also important to remember that excessive bleeding may be surgical rather than a result of failure of adequate replacement therapy. Tranexamic acid can control prolonged or intermittent bleeding after D&C or endometrial ablation and should be considered as a first line treatment before any blood products.

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